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Transpulmonary B-Type Natriuretic Peptide Uptake and Cyclic Guanosine Monophosphate Release in Heart Failure and Pulmonary Hypertension

The Effects of Sildenafil

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Objectives We sought to identify factors that discriminate heart failure (HF) patients with normal and elevated pulmonary vascular resistance (PVR) and to elucidate the role of cyclic guanosine monophosphate (cGMP)-dependent vasodilation.

Background Mechanisms of PVR increase in patients with chronic HF are incompletely understood.

Methods Twenty-two HF patients with high pulmonary vascular resistance (H-PVR) (>200 dyn·s·cm^{-5}) were compared with 24 matched low pulmonary vascular resistance (L-PVR) patients of similar age, sex, body size, HF severity, and volume status who were undergoing invasive hemodynamic study. Pulmonary arterial (PA) and venous blood samples from a wedged PA catheter were used to calculate transpulmonary B-type natriuretic peptide (BNP) uptake and cGMP release. The H-PVR patients were re-examined 1 h after a 40-mg oral dose of sildenafil.

Results Although transpulmonary BNP uptake was similar ($p = 0.2$), cGMP release was diminished in the H-PVR patients (−1.9 vs. 27.8 nmol·min^{-1}; $p = 0.005$). Transpulmonary BNP uptake and cGMP release correlated in the L-PVR patients ($R = 0.6$, $p = 0.004$) but not in the H-PVR. The H-PVR patients also had lower PA compliance, systemic arterial compliance (by 47% and 20%, $p < 0.001$ and $p < 0.03$), and cardiac index. Sildenafil reduced PVR (−47%), systemic resistance (−24%) and heart rate (−8%), increased cardiac index (+24%), and PA compliance (+87%, all $p < 0.001$), with a parallel increase of cGMP release (from −5.6 to 16.5 nmol·min^{-1}, $p = 0.047$), without affecting BNP uptake or norepinephrine$_{PA}$. The PVR response was not dependent on PA wedge pressure or pulmonary hypertension reversibility with prostaglandin E_1.

Conclusions The H-PVR patients have stiffening of both pulmonary and systemic arteries, preserved transpulmonary BNP uptake, but diminished cGMP release, which is reversible by the administration of sildenafil. This study provides in vivo evidence that phosphodiesterase 5A inhibition restores sensitivity of pulmonary vasculature to endogenous cGMP-dependent vasodilators. (J Am Coll Cardiol 2009;54:595–600) © 2009 by the American College of Cardiology Foundation

Pulmonary hypertension (PH) occurs in up to 70% of patients with moderate-to-advanced heart failure (HF) (1), adversely affecting right ventricular function, exercise capacity, and survival (2–5). Pulmonary hypertension in HF is often due to transmission of elevated left ventricular (LV) filling pressure into pulmonary circulation, but some patients also develop an elevation of pulmonary vascular resistance (PVR) (1). The mechanisms of PVR increase are incompletely understood, although structural remodeling of pulmonary vasculature and vasomotor imbalance have been implicated (6). Besides endothelin, nitric oxide, and prostaglandins, pulmonary vascular tone is regulated by natriuretic peptides (NPs) (7), which cause cyclic guanosine monophosphate (cGMP)-dependent vasodilation (8). In patients with HF, circulating NPs typically are increased, but their organ effects diminish with disease progression (9).

Decreased sensitivity of pulmonary vessels to endogenous vasodilators, reflected by low rate of local cGMP release, may explain the propensity of patients with HF to develop

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CAD = coronary artery disease
cGMP = cyclic guanosine monophosphate
HF = heart failure
H-PVR = high pulmonary vascular resistance
L-PVR = low pulmonary vascular resistance
LV = left ventricular
NP = natriuretic peptide
PA = pulmonary artery
PDE = phosphodiesterase
PGE_1 = prostaglandin E_1
PH = pulmonary hypertension
PV = pulmonary vein
PVR = pulmonary vascular resistance

PH. Whether pulmonary cGMP release differs between HF patients with low and elevated PVR has not yet been determined. To address this hypothesis, high pulmonary vascular resistance (H-PVR) patients with HF were compared with matched low pulmonary vascular resistance (L-PVR) patients. To further elucidate the link between cGMP catabolism and pulmonary hemodynamics, H-PVR subjects were also studied after the administration of the phosphodiesterase (PDE)-5A inhibitor sildenafil.

Methods

Patients with symptomatic HF due to LV dysfunction (ejection fraction <35%) with either L-PVR or H-PVR (≤200 or >200 dyn·s·cm^{-5}) (1) were examined. Subjects with L-PVR were identified from a larger HF cohort to match clinical characteristics (age, sex, body size, disease severity, and right atrial pressure) of H-PVR patients. The protocol was approved by a local ethics committee. All patients were normoxemic (oxygen saturation >90%) on room air. After signing informed consent, a pulmonary artery (PA) catheter (Braun Melsungen AG, Melsungen, Germany) was inserted under fluoroscopic guidance, and samples were acquired from the right atrium, PA, and pulmonary vein (PV). Samples of PV were obtained by aspiration from a wedged PA catheter after discarding the initial 10 ml. Only samples with an oxygen saturation >95% by blood gas analysis were accepted. Cardiac output was measured by thermodilution and systemic blood pressure with an oscillometric cuff. In the H-PVR group, the examination was repeated 1 h after an oral dose of sildenafil citrate (40 mg) (Pfizer, New York, New York).

Blood samples in ethylenediamine tetraacetic acid were immediately centrifuged (4°C) and processed. We measured cGMP by the use of radioimmunoassay (Immunotech a.s., Praha, Czech Republic) with a sensitivity of 0.2 pmol·l^{-1}, and we measured B-type natriuretic peptide (BNP) by CMIA (Architect BNP, Abbott, Abbott Park, Illinois) with sensitivity of 10 ng·l^{-1} and between-run imprecision of 6.7%. Plasma norepinephrine was measured by radioimmunoassay (CAT-combi, DRG Instruments GmbH, Marburg/Lahn, Germany).

The PVR was calculated as mean transpulmonary pressure gradient/cardiac output. Compliance was determined as stroke volume/pulse pressure (10). Transpulmonary BNP uptake and cGMP release were calculated as: (BNP_{PA} − BNP_{PV}) × cardiac output × (1 − hematocrit) and as ($cGMP_{PV}$ − $cGMP_{PA}$) × cardiac output × (1 − hematocrit), as reported previously (11).

Parameters with normal distribution (Shapiro-Wilks test) were tested by the use of paired/unpaired *t* tests and reported as mean ± SD. For abnormally distributed data (reported as medians and interquartile range), Mann-Whitney *U* or Wilcoxon tests were used. Pearson r or Spearman R (for abnormally distributed) was calculated for correlations. Nominal variables were compared between groups with the chi-square test. General linear model was used for multivariate adjustments. A p value of <0.05 was considered significant.

Results

A total of 46 subjects with HF due to coronary artery disease (CAD; n = 25) or nonischemic cardiomyopathy (n = 21) were examined; 22 (48%) were in the H-PVR group (PVR >200 dyn·s·cm^{-5}).

Determinants of increased PVR. We found that CAD tended to be more frequent in H-PVR, but other characteristics, comorbidities, medication, and procedures (coronary artery bypass grafting, device, or valve surgery) were similarly distributed (Table 1). We also found that PVR, the systemic vascular resistance/PVR ratio, transpulmonary gradient, and pulmonary pulse pressure (41 ± 12 mm Hg vs.

Table 1 Baseline Characteristics

	Low PVR (n = 24)	High PVR (n = 22)	p Value
Age, yrs	51 ± 14	54 ± 10	0.5
Male sex, %	88	82	0.6
Body mass index, kg/m^2	26 ± 5.2	27 ± 4.4	0.5
Etiology: CAD/DCM, n	10/14	15/7	0.07
NYHA functional class	2.9 ± 0.7	2.9 ± 0.6	0.8
MLHFQ score	44 ± 21	43 ± 27	0.9
Peak VO_2, ml·kg^{-1}·min^{-1}*	16.0 ± 4	14.2 ± 3	0.2
Furosemide daily dose, mg†	80 (50–101)	101 (80–160)	0.06
Hemoglobin, g·l^{-1}	135 ± 16	133 ± 20	0.7
Serum creatinine, μmol·l^{-1}	113 ± 41	113 ± 41	0.9
Diabetes/COPD/ pulmonary embolism, %	25/4/0	45/4/5	0.2/0.9/0.3
Beta-blockers/ACE or AR inhibitors, %	75/62/12	91/54/23	0.2/0.6/0.4
Spironolactone/furosemide, %	75/96	73/100	0.9/0.3
Digoxin inotropes, %	17/21	36/19	0.1/0.9
Echocardiography			
LV ejection fraction, %	23 ± 4.8	22 ± 3.5	0.4
LV end-diastolic diameter, mm	70 ± 9	70 ± 6	0.9
RV dysfunction grade, (0–3)	1.9 ± 1	2.2 ± 0.7	0.2
Mitral regurgitation grade, (0–5)	3.3 ± 0.9	3.3 ± 0.9	0.9

*Available in 12 and 12 subjects. Unpaired *t* test (mean ± SD) or †Mann-Whitney *U* test (median and interquartile range), chi-square test for nominal variables.

ACE = angiotensin-converting enzyme; AR = angiotensin receptor; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DCM = dilated cardiomyopathy; LV = left ventricular; MLHFQ = Minnesota Living With Heart Failure Questionnaire; NYHA = New York Heart Association; PVR = pulmonary vascular resistance; RV = right ventricular; VO_2 = oxygen uptake.

Table 2 Baseline Hemodynamic Parameters in HF Patients

	Low PVR (n = 24)	High PVR (n = 22)	p Value
Heart rate, min^{-1}	78 ± 15	82 ± 14	0.4
Right atrial pressure, mean, mm Hg	6.4 ± 5.7	8.7 ± 3.7	0.1
PA pressure, mean, mm Hg	24 ± 8.7	46 ± 6.4	<0.0001
PA wedge pressure, mean, mm Hg*	15.5 (8.5–25)	26.5 (22–29)	<0.0001
Transpulmonary pressure gradient, mm Hg*	7.5 (6–9)	20 (15–24)	<0.0001
PVR, dyn·s·cm^{-5}*	137 (110–171)	416 (296–607)	—
Pulmonary arterial compliance, ml·mm Hg^{-1}*	2.46 (2.0–3.3)	1.29 (0.8–1.5)	<0.0001
SVR, dyn·s·cm^{-5}	1,609 ± 502	1,750 ± 553	0.4
Systemic arterial compliance, dyn·s·cm^{-5}*	1.41 (1.2–1.7)	1.10 (0.7–1.4)	0.03
SVR/PVR ratio*	11.7 (8.1–14.7)	3.8 (3.0–4.9)	<0.0001
Systemic blood pressure, mean, mm Hg	89 ± 18	85 ± 14	0.6
Cardiac index, l·min^{-1}·m^{-2}	2.14 ± 0.4	1.83 ± 0.4	0.01

Unpaired *t* test (mean ± SD) or *Mann-Whitney *U* test (median and interquartile range).
PA = pulmonary artery; SVR = systemic vascular resistance; other abbreviations as in Table 1.

22 ± 7 mm Hg; $p < 0.0001$) were all increased in patients with H-PVR (Table 2). Pulmonary and systemic arterial compliance (Fig. 1A) were lower in patients with H-PVR. In all, PVR correlated with cardiac output, systemic vascular resistance, and PA mean and wedge pressure ($R = -0.47$, 0.34, 0.86, and 0.46, respectively).

Valid PA samples were obtained from 18 H-PVR and 19 L-PVR subjects (Table 3). The levels of BNP and cGMP correlated in the right atrium, PA, and PV of the L-PVR patients ($R = 0.5$ to 0.6; all $p < 0.05$), but not of the H-PVR ($R = 0.3$ to 0.5; all $p > 0.05$). Transpulmonary BNP uptake was similar ($p = 0.2$), but cGMP release (27.8 ± 31 nmol·min^{-1} vs. −1.9 ± 29 nmol·min^{-1}; $p = 0.005$) was significantly greater in the L-PVR patients (Fig. 2A), even after adjustment to PA wedge pressure ($p = 0.003$), diabetes, CAD, and digoxin and beta-blocker use ($p = 0.004$). In all, transpulmonary cGMP release correlated with PVR (Fig. 1B) but not with PA wedge pressure ($R = -0.1$, $p = 0.5$). Transpulmonary BNP uptake correlated with cGMP release in the L-PVR ($R = 0.62$, $p = 0.004$) but not in the H-PVR ($R = 0.1$, $p = 0.7$). Plasma norepinephrine in age-, sex-, and etiology-matched L-PVR and H-PVR subgroups ($n = 12$ and $n = 14$) were similar (2.5 ± 1.4 nmol·l^{-1} vs. 2.4 ± 0.9 nmol·l^{-1}; $p = 0.8$).

Effects of sildenafil. Oral administration of 40 mg of sildenafil to 16 H-PVR patients reduced PVR (−42%) and transpulmonary gradient (−39%) and increased cardiac index (+24%), stroke volume (+33%), and PA compliance (+87%) (Fig. 3A, Table 4). The reduction in PVR was inversely related to baseline PVR ($r = -0.71$, $p = 0.001$) and unrelated to the change of PA wedge pressure ($r = 0.02$, $p = 0.9$). Patients below and above a median of baseline PA wedge pressure had a similar PVR decrease (−254 dyn·s·cm^{-5} vs. −309 dyn·s·cm^{-5}, $p = 0.5$). We found that PA compliance had an inverse, hyperbolic relation to PVR (Fig. 3B).

According to a recent (−5 ± 27 days) clinically indicated pulmonary vasodilation test with prostaglandin E_1 (PGE_1) (alprostadil, peak rate of 275 ± 100 ng·kg^{-1}·min^{-1}), patients were labeled as having reversible (final PVR ≤240 dyn·s·cm^{-5} and TPG ≤15 mm Hg), partially reversible (only 1 criterion met), or irreversible PH (both criteria not met). The PGE_1-irreversible ($n = 8$) and completely or partially PGE_1-reversible patients ($n = 8$) did not differ by baseline PVR ($p = 0.13$), transpulmonary cGMP release ($p = 0.71$), or BNP uptake ($p = 0.71$). Sildenafil-induced

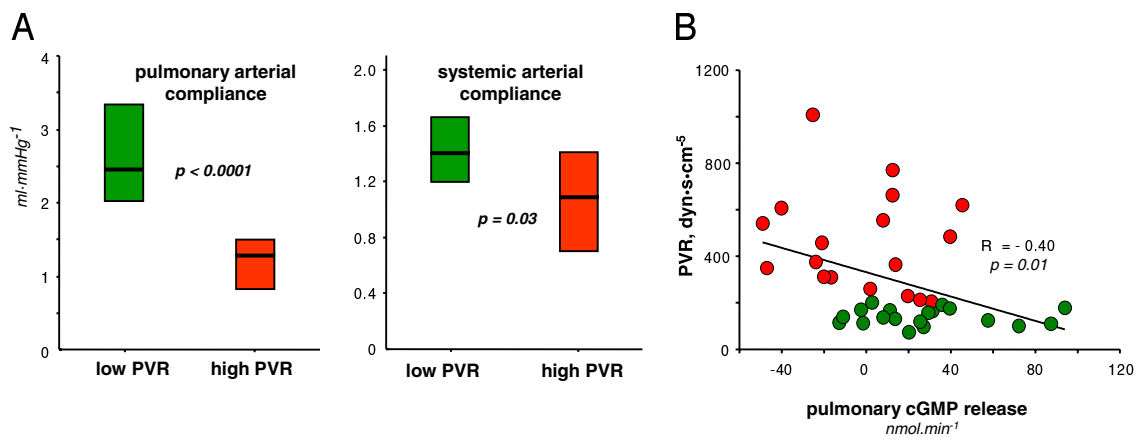

Figure 1 Pulmonary and Systemic Arterial Compliances and the Relation of PVR to Transpulmonary cGMP Release

(A) Pulmonary and systemic arterial compliance in HF patients with low or high PVR (≤200 or >200 dyn·s·cm^{-5}), median ± interquartile range. **(B)** Correlation between PVR and transpulmonary cGMP release in L-PVR **(green)** and H-PVR **(red)** patients. cGMP = cyclic guanosine monophosphate; H = high; L = low; PVR = pulmonary vascular resistance.

Table 3 Local Concentrations of BNP and cGMP at the Baseline

	RA	PA	PV	p Value RA × PA	p Value PV × RA	p Value PV × PA
BNP, ng·l^{-1}*						
L-PVR	244 (79–472)	207 (83–472)	186 (91–536)	NS	NS	0.04
H-PVR	480 (308–778)	489 (298–659)	446 (228–655)	NS	0.05	0.02
p value L-PVR × H-PVR	0.06	0.04	0.06	—	—	—
cGMP, nmol·l^{-1}						
L-PVR	12.2 ± 8	12.7 ± 11	24.2 ± 21	NS	0.005	0.0005
H-PVR	14.6 ± 7	22.2 ± 11	20.7 ± 10	0.02	NS	NS
p value L-PVR × H-PVR	NS	0.01	NS	—	—	—

Biochemical data were available from 19 low-pulmonary vascular resistance (L-PVR) and 18 high-pulmonary vascular resistance (H-PVR) subjects. Unpaired *t* test or *Mann-Whitney *U* test (columns), paired *t* test or *Wilcoxon test (lines). Values are mean (SD) or *median (interquartile range).

BNP = B-type natriuretic peptide; cGMP = cyclic guanosine monophosphate; NS = p value >0.1; PA = pulmonary artery; PV = pulmonary vein; RA = right atrium; other abbreviations as in Tables 1 and 2.

PVR response was similar in PGE_1-irreversible or -reversible (partially or completely) patients (ΔPVR: −290 ± 98 dyn·s·cm^{-5} vs. −245 ± 182 dyn·s·cm^{-5}; p = 0.54). Valid paired PA samples were obtained from 11 subjects. Sildenafil had no effect on transpulmonary BNP uptake, but it increased cGMP release (from −5.6 ± 33 nmol·min^{-1} to 16.5 ± 39 nmol·min^{-1}, p = 0.047) (Table 3, Fig. 2B). Plasma norepinephrine did not change after sildenafil (from 2.7 ± 0.6 nmol·l^{-1} to 2.4 ± 0.2 nmol·l^{-1}; p = 0.4).

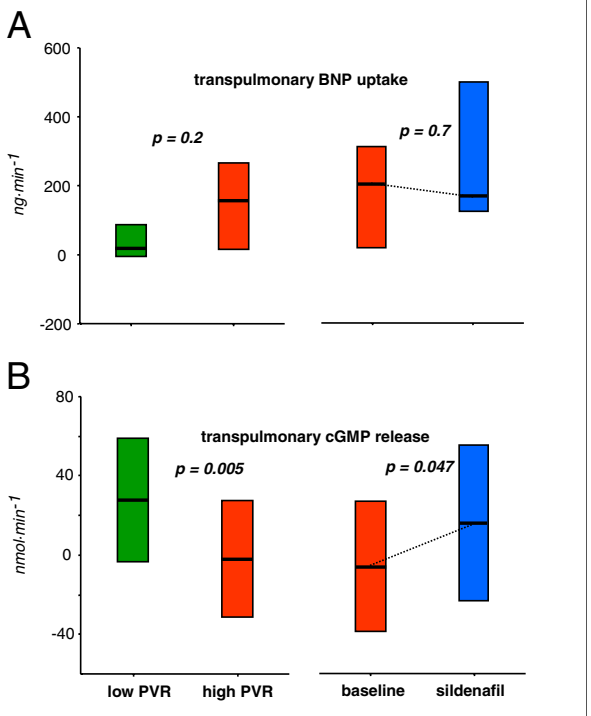

Figure 2 Transpulmonary BNP Uptake and cGMP Release

(A) Transpulmonary BNP uptake (median ± interquartile range) and cGMP release (mean ± SD) in HF patients with low or high PVR (≤200 or >200 dyn·s·cm^{-5}). **(B)** Transpulmonary BNP uptake and cGMP release in the H-PVR group before and after administration of 40 mg of sildenafil. BNP = B-type natriuretic peptide; other abbreviations as in Figure 1.

Discussion

Our first aim was to identify specific features of H-PVR patients by comparing them with their L-PVR counterparts matched for many clinical characteristics. Although pulmonary BNP uptake was similar, cGMP release was diminished in H-PVR group. Although a previous analysis (11) found that pulmonary cGMP production is uncoupled from atrial natriuretic peptide uptake in advanced HF, our study is the first to explicitly link reduced pulmonary cGMP release to high PVR in patients with HF.

Cyclic GMP serves as a mediator of vasodilation in pulmonary vessels and is synthesized by soluble guanylate cyclase (in response to nitric oxide) or by membrane-bound guanylate cyclase of the NP receptor. Because some cGMP escapes the cells by multidrug-resistance protein transporters (12), its plasma level provides an estimate of intracellular response to cGMP-dependent vasodilators.

Tissue effects of NP become attenuated with the progression of HF. This "NP resistance" is due to enhanced NP clearance, decreased NP receptor downstream signaling, or enhanced cGMP degradation by intracellular PDEs (8). The last mechanism is probably the most relevant here because cGMP-selective PDE5A is abundant in pulmonary tissue (13) and its activity further increases with HF progression (9). Marked responsiveness of PVR to PDE5A inhibition observed in this study and others (14,15) support this notion. In our study, pulmonary cGMP release correlated with BNP uptake in the L-PVR but not in the H-PVR group, indicating profound pulmonary NP resistance in the latter. This finding also explains why nesiritide therapy had no effect on the pulmonary hemodynamics in HF patients with pre-capillary PH (16). Interestingly, H-PVR patients had markedly reduced PA compliance, indicating diminished elasticity of PA tree and also lower systemic arterial compliance, suggesting that arterial stiffening affects both vascular territories.

Our second objective was to investigate the effects of sildenafil. Sildenafil reduced PVR even in patients not exhibiting PH reversibility with PGE_1 (Fig. 3A). The results are in agreement with the growing notion that even

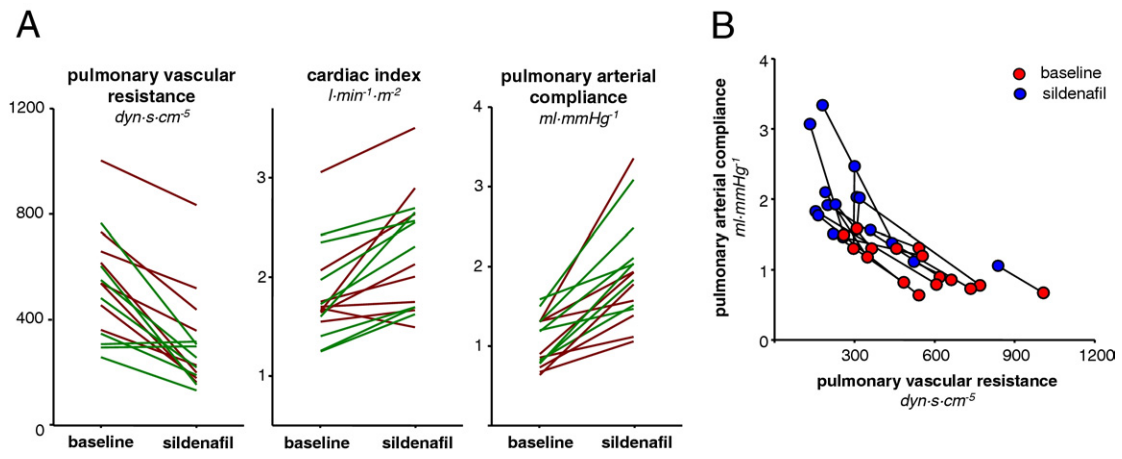

Figure 3 **Hemodynamic Responses to Sildenafil**

(A) Individual responses to 40 mg of sildenafil in H-PVR patients. **Red lines** = PGE_1-irreversible PH; **green lines** = PGE_1-reversible PH (partially or completely). **(B)** Relation of pulmonary arterial compliance to PVR before **(red)** and after **(blue)** sildenafil. PGE_1 = prostaglandin E_1; PH = pulmonary hypertension; other abbreviations as in Figure 1.

"fixed" PVR elevation in many HF patients is eventually reversible after prolonged LV unloading (17) or perhaps with pulmonary-selective vasodilators. The PVR reduction was also independent of baseline PA wedge pressure or its change. Although long-term elevation of left atrial pressure can increase PVR, particularly in mitral stenosis (18), our data do not indicate that actual LA pressure has a direct role in acute pulmonary vasomotor response to sildenafil.

Table 4 **Effect of 40-mg Sildenafil Dose in H-PVR Patients**

	Baseline	Sildenafil	p Value
Heart rate, min^{-1}	81 ± 15	74 ± 12	0.003
PA pressure, mean, mm Hg	48 ± 6	37 ± 8	<0.001
PA wedge pressure, mean, mm Hg*	26 (22–29)	25 (19–27)	0.20
PVR, $dyn{\cdot}s{\cdot}cm^{-5}$	341 (356–641)	243 (185–339)	<0.001
Transpulmonary pressure gradient, mm Hg*	23 (19–26)	12 (10–18)	<0.001
Pulmonary arterial compliance, $ml{\cdot}mm\ Hg^{-1}$*	1.03 (0.8–1.3)	1.9 (1.5–2.1)	<0.001
SVR, $dyn{\cdot}s{\cdot}cm^{-5}$	1823 ± 593	1352 ± 455	<0.001
SVR/PVR ratio*	3.7 (2.9–4.0)	5.2 (3.4–6.3)	0.002
Systemic blood pressure, mean, mm Hg	86 ± 12	79 ± 10	0.003
Cardiac index, $l{\cdot}min^{-1}{\cdot}m^{-2}$	1.8 ± 0.4	2.2 ± 0.6	<0.001
Stroke volume, ml	46 ± 14	61 ± 15	<0.001
BNP, $ng{\cdot}l^{-1}$*			
RA	525 (365–768)	403 (317–732)	0.6
PA	543 (298–659)	458 (375–759)	0.6
PV	514 (228–581)	378 (263–640)	0.7
cGMP, $nmol{\cdot}l^{-1}$			
RA	14.7 ± 7.7	14.4 ± 6.7	0.9
PA	24.5 ± 13	18.8 ± 6.9	0.03
PV	20.6 ± 11	24.6 ± 14	0.4

Paired *t* test or *Wilcoxon test. Mean ± SD or *median (interquartile range) are reported. Paired biochemical data were available from 11 subjects.

Abbreviations as in Tables 1 to 3.

Sildenafil markedly affected PA compliance, a parameter that characterizes elasticity of pulmonary arterial tree and pulsatile loading of the right ventricle. The nonlinear, hyperbolic relationship between PVR and PA compliance (Fig. 3B) suggests that relatively small change of PVR after sildenafil may be associated with large increase in PA compliance, particularly among patients within lower PVR range. In idiopathic PH, PA compliance is a strong predictor of mortality (19), so its improvement in HF patients might impact prognosis as well.

Sildenafil increased cardiac index (+24%), mainly by increasing stroke volume. Greater contractility, reduced afterload, or diminished interventricular interaction (20) could be involved, but the latter 2 mechanisms are more plausible than the former. Previously, sildenafil did not change LV dP/dt_{max} in HF patients with PH (15), and it actually blunted dobutamine-stimulated contractile response in healthy adults (21). Although sympathetic activation and increase of plasma norepinephrine after sildenafil was described in healthy volunteers (22), this report and another (23) show no such evidence in patients with HF.

Several short-term studies in HF patients (2,14,24) recently showed favorable effects of sildenafil on pulmonary hemodynamics, exercise tolerance and quality of life without serious side effects. Therefore, PDE5 inhibitors seem to be promising drugs for selected HF patients, particularly in peritransplant settings, but long-term safety remains unknown, and they require testing before their use in the general HF population.

Study limitations. First, pulmonary cGMP production was estimated from spillover into the bloodstream, and this approach likely underestimates intracellular changes. Transpulmonary cGMP release was even negative in some

subjects, which may reflect the assay variation but also intravascular degradation or cellular reuptake of cGMP (12). Second, the sample size is relatively small, and type 2 error limits more detailed analyses. Third, groups were not completely balanced in some covariates, but they differed in cGMP release even after multivariate adjustments. Fourth, some have argued that the transpulmonary gradient is a more appropriate measure of forces opposing blood flow than PVR (25). When data were reanalyzed with the use of a 12-mm Hg transpulmonary gradient cut-off instead of a PVR cut-off, the main findings of the study remained unchanged.

Conclusions

Patients with HF and increased PVR are characterized by increased stiffness of systemic and pulmonary arteries, preserved transpulmonary BNP uptake, but diminished cGMP release that is reversible by acute PDE5A inhibition. This study provides human in vivo evidence that the use of sildenafil restores sensitivity of pulmonary vasculature to endogenous cGMP-dependent vasodilators.

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